

REMARKS

Applicants submit this Amendment to insert the required references to SEQ ID NOS of the Sequence Listing filed on July 13, 1998.

The Examiner has rejected claims 69 to 76 as allegedly obvious over Hirata, Kishimoto, Oi and Morrison. Applicants respectfully traverse the rejection.

Hirata and Kishimoto only teach <u>human</u> IL-6R and hybridomas producing these antibodies. The Oi and Morrison references generally teach chimeric antibodies using murine variable regions. However, these references fail to teach the unexpected and superior properties of inhibition of multiple myeloma cell growth demonstrated by the claimed chimeric antibodies.

For example, K. Sato et al., Cancer Research, Vol. 53, p. 851 - 856, 1993 (enclosed), page 852, right column, line 3 from the bottom - page 854, the left column line 1, describes that "The concentrations of the reshaped human PM-1 antibody which inhibited 50% cell growth i.e., IC_{50} , were 90 ng/ml (S6B45), 100 ng/ml (ILKM3), and 0.8 μ g/ml (MMS1) in this assay" referring to Fig. 5. In this case, the cell growth means

"multiple myeloma cell growth" (see page 852, the right column, lines 6 to 3 from the bottom). Namely, the above-cited part describes that the reshaped human PM-1 antibody inhibits the growth of multiple myeloma cells. However, Fig. 5 also compares mouse monoclonal antibody PM-1 (hollow triangles), chimeric PM-1 (hollow circles) and reshaped human PM-1 antibody (solid circles) on the growth of the multiple myeloma cells. As can be seen from Fig. 5, cell growth inhibitory activity of the chimeric antibody PM-1 is substantially the same as that of the reshaped human antibody PM-1. Therefore, it is clear that the present chimeric antibody PM-1 is effective to inhibit multiple myeloma cell growth.

Furthermore, K. Sato et al., Molecular Immunology, Vol. 31, No. 5, p. 371 - 381, 1994 (enclosed), page 379, the right column, lines 9 to 18 states that "The IC₅₀S of the reshaped human AUK12-20 antibodies were almost equal to those of mouse and chimeric AUK12-20 antibodies (approximately 40 ng/ml for KT3 cells, 50 ng/ml for ILKM3 cells and 800 ng/ml for MMS1 cells) . . . These reshaped human AUK12-20 antibodies, therefore, could be efficacious in human patients with IL-6 related disorders". Since the IC₅₀ of the reshaped human AUK12-20 antibody is about equal to that of the chimeric AUK12-20 antibody, chimeric AUK12-20 antibody should be efficacious in human patients with IL-6 related disorders. In addition, it is clear that the chimeric antibody is efficacious in human patients with IL-6 related disorders, with reduced immunogenicity.

In comparison with the IC_{50} of the chimeric antibody PM-1, included in the present invention, and that of the chimeric antibody AUK12-20, the IC_{50} of the chimeric antibody PM-1 against ILKM3 cells is 100 ng/ml, while that of the chimeric antibody AUK12-20 against the same cells, ILKM3, is 500 ng/ml. Namely, the multiple myeloma cell inhibitory activity of the chimeric antibody PM-1 is 5-times higher than that of the chimeric antibody AUK12-20.

The higher activity of the chimeric antibody PM-1 over that of AUK12-20 cannot be expected, especially from comparison of the properties of the corresponding parent mouse monoclonal antibodies PM-1 and AUK12-20. Therefore, chimeric PM-1 provides unexpected and remarkable properties against IL-6 related disorders. The applied references are silent as to these unexpected properties. Accordingly, the applied references fail to provide motivation to use IL-6 as a standing monoclonal antibody for construction of a chimeric antibody.

Finally, as can be seen from T. Tsunenari et al., Anticancer Research, Vol. 16, p. 2537 - 2544 (1996) (enclosed), page 2542 Figs. 6 and 7, the chimeric antibody PM-1

exhibits <u>in vivo</u> anti-tumor action against S6B45 multiple myelomal cells in exograft model of athymic nude mice. In Figs. 6 and 7, the chimeric antibody PM-1 exhibits anti-tumor activity substantially at the same level as that of the reshaped human antibody PM-1 and mouse monoclonal antibody PM-1. The applied references are also silent as to the *in vivo* efficacy demonstrated by the claimed chimeric antibodies.

All of the above references were published <u>after</u> the instant priority date. Thus, at the time of the invention, it was unexpected that a chimeric IL-6 antibody would have activity substantially equal to that of humanized antibody. Therefore, there was no reasonable expectation of success that a chimeric antibody would be effective based only on the known activity of the corresponding mouse antibody.

Furthermore, the references cited by the Examiner fail to provide any motivation to make the instant IL-6 chimeric antibodies since the references fail to teach or suggest their superior and unexpected properties against IL-6 related disorders. Therefore, the applied references fail to teach or suggest instant invention. Accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

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Date

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Respectfully submitted,

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